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(54) Title: SYNERGY OF DOPAMINE D2 AND ADENOSINE A2 RECEPTORS ACTIVATES PKA SIGNALING VIA BETA/GAMMA DIMERS

(57) Abstract: This invention pertains to the discovery that a dopamine receptor agonist can activate PKA signaling and/or can act synergistically with an adenosine receptor to activate such signaling. In various embodiments, this invention exploits the synergy between the dopamine receptor pathway and an adenosine receptor pathway to provide methods of mitigating one or more symptoms produced by the chronic consumption of a substance of abuse or to mitigate one or more physiological and/or behavioral symptoms associated with cessation of chronic consumption of a substance of abuse. In certain embodiments, the methods involve administering to the mammal an effective amount of an adenosine receptor antagonist; and an effective amount of a dopamine receptor antagonist; where the effective amount of the adenosine receptor antagonist is lower than the effective amount of an adenosine receptor antagonist administered without said dopamine receptor antagonist.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US03/09629.

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 1/00; A01N 61/00; A61K 31/00  
US CL : 435/810, 811, 812; 514/1

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/810, 811, 812; 514/1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOUCH, M. et al., Regulation of sensorimotor gating by interactions of dopamine and adenosine in the rat, Behavioural Pharmacology, 1998, Vol 9, No 1, pages 23-29, see the Abstract and Experiment 1 on page 24.	21-35, 58-77, 134-149
A	MAILLIARD-W.S. et al., Recent advances in the neurobiology of alcoholism: the role of adenosine, Pharmacology & Therapeutics, 2004, Vol 101, pages 39-46, see the entire article.	1-149
A	WALTER, H. et al., Dopamine and Alcohol Relapse: D1 and D2 Antagonists Increase Relapse Rates in Animal Studies and Clinical Trials, Journal of Biomedical Science, 2001, Vol 8, pages 83-88, see the entire article.	1-149

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

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**INTERNATIONAL SEARCH REPORT**

PCT/US03/09629

**Continuation of B. FIELDS SEARCHED Item 3:**

STN: MEDLINE, BIOSIS; West 2.1

search terms: Dopamine, D1, D2, adenosine, A1, A2A, agonist, antagonist, synergy, cooperativity, PKC, PKA, beta-gamma, translocation, accumbens, striatal, VTA, reinforcing, addiction, abuse, ethanol, opiate, cannabinoid, NG108-15